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ACID-BASE HOMEOSTASIS IN THE HUMAN SYSTEM

A Study Report

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I. Introduction

Homeostasis, which has been termed "the central theorem of the physiology of the intact higher animal organism" (1), is manifest continually in the human through the response of the total collection of subsystems of the body to normal and abnormal challenges. One of the most vigorously defended parts of the human system concerns acid-base balance and pH regulation, presumably because of the importance of such regulation to the myriad of biochemical reactions occurring in the cells (2). Indeed, death follows with certainty, if pH regulation is not maintained at near normal capacity.

Acid-base regulation is a cooperative phenomena *in vivo* with body fluids, extracellular and intracellular buffers, lungs, and kidneys all playing important roles. The present account is much too brief to be considered a review of present knowledge of these regulatory systems, and should be viewed, instead, as a guide to the elements necessary to construct a simple model of the mutual interactions of the acid-base regulatory systems of the body. More detailed information is available elsewhere (1, 3-8).

II. Cells

Whole-body intracellular space is an extremely inhomogenous fraction of the body with wide diversity in both function and form. In an ideal sense only, which may be useful as a first approximation, however, cell space may be characterized by average results weighted in some appropriate manner.

Thus, metabolic reactions in the cells produce large quantities of carbon dioxide and smaller quantities of other acid end products. It is estimated that normal metabolic formation of carbon dioxide is approximately

200 ml/min (STPD) or 8.98 mmol/min (1 mmol CO_2 = 22.26 ml CO_2), while production of other acids amounts to only 50-100 mmol/day, or 0.035 - 0.07 mmol/min (9). The cells contain chemical buffer systems capable of serving as intermediate storage reservoirs of these acid end products, but in a normal balance situation the acid produced is transmitted to the interstitial fluid and thus to the blood to be excreted by the lungs and kidneys.

The main chemical buffers of the cells are proteins, organic phosphates, bicarbonate, and bone carbonate. Bone is generally differentiated from other intercellular forms and considered by itself. The contribution of bone to acid-base homeostasis is potentially large but generally not well understood except in extreme cases (10). Bone will be treated only cursorily in most of what follows. Concentrations appropriate to tissue intracellular space (not bone) appear to be (11)

bicarbonate: 10 mmol/L,
phosphates: 100 mmol/L,
proteins: 60 mmol/L.

In view of the fact that intracellular volume is approximately 25 L, the stores of cellular buffer anions are large.

The red blood cells, (erythrocytes) have their own distinct function to perform in acid-base control and they will be considered in more detail in the section on blood. Their volume is approximately 2 L, although the water content of red cells is only 1.3 L, if a protein content of 35% is assumed.

During acute and chronic attacks of both respiratory and metabolic (non-carbon dioxide) components of acid-base balance, there is no doubt about the participation of the cell in homeostatic response (12-16), but the nature of the response in some cases is mechanistically unclear (17). This point will be discussed later in relation to a simple model.

Under the normal conditions, the average pH of the cell seems to be

about 7.0 (18). The cell membrane is generally assumed to be highly permeable to carbon dioxide gas with the P_{CO_2} 45-50 mm Hg at equilibrium. The permeability of the membrane to bicarbonate or hydrogen ions is generally regarded as being somewhat less (6, 19, 20).

III. Interstitial Fluid

The interstitial fluid which lies between the cells consists of a small amount of free fluid (0.5 L) and a large portion held in a gel (11.5 L). For most purposes connected with acid base balance, the interstitial fluid behaves as if the water were all free. Almost all dissolved substances, with the exception of protein, move freely between the plasma and the interstitial fluid through the capillary pores and perfect mixing can generally be assumed for most substances. In this way, the cells are able to communicate almost directly with other parts of the body through the blood. In a similar way, the plasma has a large reservoir of materials at its disposal to assist in "buffering" changes which occur locally. Thus, with the exception of protein, the constituents of interstitial fluid should be very similar to plasma. This is indeed found to be the case, but the concentration of various ions are unequal in interstitial space and plasma due to the Donnan or Gibbs-Donnan effect. It is easy to show that in the presence of a non-diffusable charged ion on one side of a membrane, all other diffusible charged ions (not pumped or otherwise effected) must distribute themselves unequally on the two sides of the membrane (21).

The only buffer of any real significance in interstitial space is bicarbonate whose concentration in interstitial water is determined from the corresponding concentration in plasma water by the relation

$$[HCO_3^-]_{ISF} = r\,[HCO_3^-]_P \qquad (1)$$

where $[\cdots]$ denotes concentration in mmol/L H_2O and r is the experimentally

determined Donnan factor, generally assumed to be 1.05 for anions (21). Note that the concentrations here are relative to liters (∿ kilograms) water, not plasma volume. Thus, due to the presence of 7% protein in plasma $V_{P,\ H_2O} = 0.93\ V_P$. For interstitial fluid (2% protein) the correction is usually negligible.

A second buffer system exists in interstitial fluid, the phosphate system ($H_2PO_4^-$, $HPO_4^=$). The total buffering power of this system is usually negligible in comparison with the bicarbonate system in vivo and will generally be neglected in what follows. Less than 1% of the buffering is accomplished by the phosphate system in most circumstances.

IV. Blood

Blood consists of two parts, an extracellular fluid of about 3 L volume and 7% protein, and a cellular part of about 2 L volume and 35% protein. The red cell membrane is permeable to all normal ionic species except protein.

The major constituents of plasma relative to acid-base functions in vivo are bicarbonate and protein. Both of these substances act as buffers for hydrogen ion changes, with the bicarbonate being the more important. Plasma concentrations of bicarbonate and the various protein forms differ in the various parts of the systemic circulation due to local changes in relative portions of oxygen, carbon dioxide, and hydrogen ion carried in the blood. In normal arterial plasma, pH = 7.4, $[CO_2]$ = 1.2 mmol/L, and $[HCO_3^-]$ = 24 mmol/L, on the average. In venous plasma, typical figures might be pH = 7.37, $[CO_2]$ = 1.35 mmol/L, and $[HCO_3^-]$ = 25.1 mmol/L

Erythrocytes, on the other hand, contain hemoglobin in addition to bicarbonate, and it is hemoglobin which plays the principal role in carbon

dioxide, as well as oxygen, transport. On the average, 34 g. of hemoglobin is contained in 100 ml. of red cells and with a normal hematocrit of about 40, blood usually contains about 15 g. of hemoglobin per 100 ml. These values may have considerable local variation. The protein hemoglobin in vivo has a net negative charge. It is capable of combining with, and thereby transporting, both oxygen and carbon dioxide, and at the same time is capable of buffering hydrogen ions. The molecular weight of hemoglobin is approximately 68,000 g. and one mole of hemoglobin is capable of combining with four moles of oxygen. It is usual to measure hemoglobin amounts either in grams or in milliequivalents on an oxygen basis. Thus, 1 mole of hemoglobin contains 4 equivalents of hemoglobin (or 1 milliequivalent weight(meq) of hemoglobin = 16.7 g.). Hemoglobin combined with oxygen to its fullest extent is called oxyhemoglobin and will be denoted "HbO_2" while hemoglobin carrying no oxygen is called reduced hemoglobin and will be denoted "Hb". The negative charge will be suppressed. Each gram of hemoglobin is capable of carrying approximately 0.06 mmol of oxygen (or 1.34 ml STP) at full saturation. The fraction saturation of hemoglobin is the fraction of hemoglobin in the blood that is in the form HbO_2. This fraction varies from 0.97 for arterial blood down to about 0.70 for venous blood (under normal resting conditions). The relation between the saturation level (usually expressed as per cent saturation) and the oxygen partial pressure is expressed by the oxygen dissociation curve of hemoglobin (22).

In general, a buffered solution is one which tends to maintain a constant pH in the face of challenge by acid additions or withdrawals. Such a solution contains appreciable concentrations of various weak acids and their corresponding highly ionized "salts". For example, consider a solution containing 0.1 mole/L sodium acetate and 0.05 mole/L acetic acid (at 25°C).

The pH is approximately

$$pH = 4.57 + \log \left[\frac{0.1}{0.05}\right] = 4.87.$$

Addition of 0.01 mole of hydrochloric acid to a liter of this solution would lead to an approximate new pH given by

$$pH = 4.57 + \log \left[\frac{0.09}{0.06}\right] = 4.75.$$

Addition of this same quantity of acid to a liter of pure water (pH = 7.) leads to a new pH of 2. The resistance of the buffer solution to pH changes is clear.

As stated above hemoglobin serves as a buffer (not the only one) in blood. In fact both oxyhemoglobin and reduced hemoglobin have buffering abilities. The presence of oxygen makes the oxyhemoglobin a stronger acid than reduced hemoglobin and consequently the reduced hemoglobin is a better buffer than oxyhemoglobin. The body uses this fact to good advantage since oxygen is given up and acidic waste picked up in the tissue. The buffering ability of a solution is generally expressed by means of its titration curve which is the relation between the amount of acid added to the solution and the pH of the solution. The experimentally important variable is the slope of the titration curve and the term "buffer value" is usually defined as the negative of the slope of the titration curve (5). The units of buffer value are usually mmol/liter/pH unit and this unit is termed a slyke (sl) (5). The buffer value of a solution containing more than one buffer substance is the sum of the buffer value of each substance. The buffer value of each substance is directly proportional to the concentration of that substance.

Transportation of carbon dioxide from the tissues to the lungs is effected by both the plasma and the red cells. In general, carbon dioxide diffuses through the interstitial space into the plasma and red cells. A small amount of carbon dioxide gas dissolves in the plasma and an even smaller

amount forms a direct carbamino compound with plasma proteins. Some of the dissolved CO_2 reacts with water to form carbonic acid which ionizes slightly

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-. \qquad (2)$$

The carbon dioxide diffusing into the erythrocytes remains partially dissolved but the largest portion of that which enters either combines directly with hemoglobin to form carbamino - CO_2 or hydrolyzes under carbonic anhydrase catalysis to form carbonic acid which ionizes to a great extent. This ionization takes place because the H^+ ions produced are buffered by the hemoglobin, and then the HCO_3^- ions largely diffuse back into the plasma. The carbonic anhydrase present allows the hydrolysis reaction to proceed sufficiently rapidly that equilibrium is attained almost instantaneously. Thus, the major forms of carbon dioxide in the plasma are dissolved carbon dioxide and bicarbonate, and in the red cell are dissolved carbon dioxide, carbamino - CO_2, and bicarbonate. Typical average values for carbon dioxide distribution in one liter of normal arterial blood would be

Plasma: HCO_3^- = 14.40 mmol

CO_2 (dissolved) = 0.72 mmol

Red Cell: HCO_3^- = 4.83 mmol

CO_2 (dissolved) = 0.40 mmol

Carbamino-CO_2 = 1.00 mmol

In normal venous blood corresponding values would be

Plasma: HCO_3^- = 15.06 mmol

CO_2 (dissolved) = 0.81 mmol

Red Cell: HCO_3^- = 5.33 mmol

CO_2 (dissolved) = 0.45 mmol

Carbamino - CO_2 = 1.50 mmol

Thus plasma bicarbonate is the major carbon dioxide carrier, but the distri-

bution depends greatly on the presence of the red cell with its carbonic anhydrase and hemoglobin.

V. Respiratory System

The major acid end product of metabolism, carbon dioxide, is produced by the body at the rate of about 200 ml/min at rest. Each day a minimum of about 300 liters of carbon dioxide is generated and in a steady state precisely this amount must be disposed of. It is one of the major functions of the respiratory system to effect this disposal. By the respiratory system is meant the lungs together with their controlling center in the brain and nervous system. Normally, except during exercise, arterial P_{CO_2} is the main stimulus to control of alveolar ventilation. This stimulus appears to be due to neural impulses transmitted from two distinct sets of receptors: central receptors located in the brain-cerebrospinal fluid region, and in peripheral receptors located mainly in the carotid and aortic bodies (23, 24). The exact cause of the stimulus is difficult to determine, but either P_{CO_2} itself or hydrogen ion level (in a non-hypoxic state) would suffice with hydrogen ion level more likely centrally. The peripheral receptors seem to account for somewhat less of the respiratory response than the central receptors.

Basically, if arterial P_{CO_2} rises, arterial hydrogen ion levels increase slightly which stimulates the peripheral receptors to increase firing and stimulate respiration to some extent. The major response, in this case, is due to the response of the central receptors. An increase in arterial P_{CO_2} causes a P_{CO_2} shift in the interstitial fluid of the brain due to the lipid solubility of carbon dioxide. Cerebrospinal and interstitial fluid are not as well buffered as the blood and a barrier to rapid exchange of buffers (mainly bicarbonate) between these systems prevents ion equilibration from occurring rapidly. Thus the P_{CO_2} increase in the central area causes

a much larger hydrogen ion change there and a correspondingly larger increased stimulation to ventilation. This stimulation disappears with time as bicarbonate adjustments are made which allow the pH to return to normal and the main stimulus reverts to the peripheral receptors. The increased ventilation tends to reduce the arterial P_{CO_2} completing the feedback loop.

When hydrogen ion concentration rises peripherally due to addition of nonvolatile acid, alveolar ventilation is stimulated because of the increased activity of the peripheral receptors. The fall in carbon dioxide levels is transmitted centrally and causes a competitive depression of the ventilation. As time passes, central adjustments in bicarbonate levels are made which allow alveolar ventilation to increase. This increase in ventilation tends to drive arterial pH back to normal.

VI. Renal System

Addition of acidic substances other than carbon dioxide or of substances with basic properties to the blood causes deviations in hydrogen ion, bicarbonate and carbon dioxide levels from normal and compensation for these deviations cannot be completely made by the buffering systems of the body discussed up to now (the respiratory system may be considered of a physiological buffer). It is the role of the renal system to effect complete compensation. The active, constant role the kidney plays even in normal states is, in fact, large and important. With a normal glomerular filtration rate of 125 ml/min and a plasma bicarbonate level of 24 mmol/l, 3 millimoles of bicarbonate are filtered each minute. If this were not almost completely reabsorbed, the body would rapidly be depleted of one of its most important chemical buffers. In fact, bicarbonate seems to be completely reabsorbed, in effect, by the body in the normal state.

Renal reabsorption of bicarbonate is accomplished as a result of the interaction between hydrogen ion actively secreted by the tubules and filtered bicarbonate with consequent diffusion of the resulting carbon dioxide back into the cells where hydration leads to bicarbonate reformation. The source of the original hydrogen ions secreted is not clear, but it is clear that the process is extremely carbon dioxide sensitive. On a phenomenological level, the renal clearance (excretion rate/plasma concentration) of bicarbonate appears to exhibit a threshold occurring at a plasma concentration of approximately 24 - 28 mmol/1. The maximal tubular reabsorptive capacity per unit volume of glomerular filtrate thus determined is about 2.4 - 2.8 meq/100 ml of glomerular filtrate with arterial P_{CO_2} = 40 mm Hg and increases with increasing arterial P_{CO_2}. This apparent threshold now seems to be an artifact of the experimental technique used in its measurement and the current view is that a complex interaction between extracellular volume, potassium, and adrenal steroids control bicarbonate reabsorption (25).

The kidney's fundamental method of reaction to increased acid loads in the body must be such as to not only reabsorb filtered bicarbonate but also to generate new bicarbonate at an enhanced level. During an acid load plasma-bicarbonate level falls and hence filtered bicarbonate decreases. Acid secretion (hydrogen ion) by the tubules continues at a relatively enhanced level determined by blood P_{CO_2}. For each hydrogen ion secreted a bicarbonate ion is generated in peritubular blood. The secreted hydrogen ions are transported to the urine by formation of ammonium ions and by combination with phosphate buffers. Thus the acidosis is corrected. The process continues until the normal state is attained (if possible), but total com-

pensation takes from one to several days. With an increasing base load, plasma bicarbonate rises increasing filtered bicarbonate. Once acid secretion is exceeded, progressive amounts of bicarbonate are lost directly in the urine and correction follows.

VII. Acid-Base Abnormalities

Modern clinical terminology for disturbances in acid-base regulation is as follows (5). Acidosis refers to an abnormal physiological process characterized by gain of acid or loss of base by the extracellular fluid of the body. Alkalosis is an abnormal physiological process characterized by gain of base or loss of acid by the extracellular fluid of the body. The prefix metabolic (metabolic acidosis, metabolic alkalosis) is used to denote abnormal processes characterized by primary gains or losses of strong acid, strong base, or bicarbonate from the extracellular fluid. The prefix respiratory (respiratory acidosis, respiratory alkalosis) refers to abnormal processes in which there are primary changes in the rate of alveolar ventilation relative to the rate of carbon dioxide production.

Abnormalities in blood acid-base parameters, which are taken to be pH, bicarbonate concentration, and P_{CO_2} of plasma, are characterized by the following terms. Acidemia means pH is lower than normal. Alkalemia means pH is higher than normal. Hypobasemia means bicarbonate concentration is lower than normal while hyperbasemia means bicarbonate concentration is higher than normal. Hypocapnia and hypercapnia refer to a decreased or increased level of P_{CO_2} relative to normal.

The abnormal physiological processes, acidosis and alkalosis, may lead to a variety of different abnormalities in the blood acid-base parameters due to the secondary or compensatory reactions of the body to the primary disturbance.

A gain of strong acid or a loss of strong base or bicarbonate from the extracellular fluid all lead to a fall in the concentration of bicarbonate in the extracellular fluid. This fall is the prime abnormalitity of metabolic acidosis. In acid loading the bicarbonate level falls because of the buffering of the acid by the bicarbonate. The body responds to this loss of bicarbonate in several ways. The cell fluids effectively transfer bicarbonate into the extracellular space either directly by bicarbonate movement or indirectly by hydrogen ion uptake or by both processes. The respiratory system responds by adjusting P_{CO_2} to a lower value. The renal system responds by effectively generating new bicarbonate through acid secretion.

In metabolic alkalosis the primary disturbance is due to a gain of bicarbonate or loss of acid (gain of base) by the extracellular fluid. Since the loss of acid is buffered by the bicarbonate system, in either case a gain of bicarbonate occurs. Cells respond by transferring hydrogen ions into extracellular fluid thus eliminating some bicarbonate. The respiratory system increases P_{CO_2}. The renal system rather rapidly raises excretion of bicarbonate.

In respiratory acidosis, alveolar ventilation is decreased relative to the rate of carbon dioxide production. Carbon dioxide levels in the body increase leading to a fall in pH. The buffer systems respond to the decreased pH and bicarbonate levels increase. The kidney increases its excretion of titratible acid and ammonia and thus raises bicarbonate levels even further. These responses tend to raise pH.

With respiratory alkalosis, alveolar ventilation rises relative to carbon dioxide production leading to a primary loss of carbon dioxide. This causes pH to rise. The buffer system acts to retard the rise by reducing

bicarbonate levels in the body and the renal system by excreting bicarbonate in the urine. In this way pH tends to fall.

VIII. A Simple Model

In this section a quantitative approach to acid-base homeostasis is presented which incorporates much of the data and experimental findings outlined in the preceding sections. This approach will utilize a modeling format as it is intended to include the resultant model as a subsystem model in a more complete analysis of overall circulatory regulation. In fact, the current intention is to use a presently available circulatory model (26) as the main component of a much larger model with systems such as the acid-base homeostatic system discussed here being added at a later date. With this in mind, many circulatory variables may be assumed known as the large model will provide values for these. Such variables include cardiac output, hematocrit, oxygen consumption, cell volume, etc. A second point worthy of mention in this connection is the fact that the overall model is basically designed for the study of intermediate to long term effects and that the present model must be adequate for the representation of experiments of days to weeks duration. Previous models which have considered acid-base response have not been adequate for simulation of even a one day response.

The present model consists of a compartmental approach with seven distinct compartments. These are chosen as lungs, brain, cerebrospinal fluid, tissue (non-brain) intracellular space, tissue (non-brain) extracellular space, arterial blood and mixed venous blood. The kidneys are represented explicitly only in their effect on bicarbonate reabsorption and new bicarbonate production. The assumption is made that the carbon dioxide buffer

curve (or equivalently the carbon dioxide dissociation curve) represents the steady-state situation and serves also as an adequate predictor of the steady state during transient events. Hypoxia will not be of interest here and the dynamics of the oxygen system will be kept very simple, just as they are in the large circulatory model.

To begin with, consider the situation in the tissue (non-brain) intracellular space (IC). Let B_{IC} represent the bicarbonate concentration of this compartment in mmol/l, P_{IC} the partial pressure of CO_2 in mm Hg, MC_{IC} the total metabolic production of CO_2 in all forms in mmol/min, MH_{IC} the effective net metabolic rate of formation of hydrogen ion in mmol/min, W_{IC} the total concentration of CO_2, BS_{IC} the concentration of bicarbonate at pH = pHS_{IC}. Corresponding definitions hold for tissue (non-brain) extracellular space and the subscript EC is used to denote these. Then the conservation equations become

$$\frac{d}{dt}[V_{IC}\, W_{IC}] = MC_{IC} + k_1(P_{EC} - P_{IC}) + k_2(B_{EC} - B_{IC}) - MH_{IC}, \tag{3}$$

and

$$\frac{d}{dt}[V_{IC}\, BS_{IC}] = k_2(B_{EC} - B_{IC}) - MH_{IC}. \tag{4}$$

These equations are to be used in conjunction with the CO_2 buffer or dissociation equation for the compartment which is

$$W_{IC} = BS_{IC} - \beta_{IC}\left\{pH_{IC} - pHS_{IC}\right\} + A_{IC}P_{IC} \tag{5}$$

where

$$pH_{IC} = pK_{IC} + \log\left[\frac{W_{IC} - A_{IC}\,P_{IC}}{A_{IC}\,P_{IC}}\right]. \tag{6}$$

The first term on the right side of Equation (3) represents metabolic production of CO_2, the second term represents diffusion of CO_2 from extracellular space, the third term represents "net effective bicarbonate flux" from extracellular space, and the last term represents "net metabolic hydrogen ion production". The effect of these last two terms is to raise or lower the bi-

carbonate concentration at fixed pH and Equation (4) represents this fact. In Equation (5) the total carbon dioxide concentration is obtained by summing the bicarbonate concentration and the non-bicarbonate CO_2 concentration. Bound CO_2 amounts (carbamino compounds) are assumed negligible here. The slope of the CO_2 titration curve is given by β_{IC} and is assumed constant for this compartment. Note that

$$B_{IC} = BS_{IC} - \beta_{IC} \{pH_{IC} - pHS_{IC}\}. \tag{7}$$

Typical values for the constants appear to be $k_1 = 3.0$, $k_2 = 0.0027$, $pHS_{IC} = 7.0$, $A_{IC} = 0.03$, $pK_{IC} = 6.1$, and $\beta_{IC} = 15$. These values were chosen so that when $MC_{IC} = 9.0$, $MH_{IC} = 0.04$, $P_{EC} = 45$, and $B_{EC} = 25.87$ a steady state obtains with $B_{IC} = 11.3$, $P_{IC} = 48.$, and $pH_{IC} = 7.0$. For the tissue (non-brain) extracellular space (EC), the conservation equations become

$$\frac{d}{dt}[V_{EC}\, W_{EC}] = Q_{EC}(W_{AB} - W_{VB}) - k_1(P_{EC} - P_{IC}) - k_2(B_{EC} - B_{IC}) + R_B, \tag{8}$$

and

$$\frac{d}{dt}[V_{EC}\, BS_{EC}] = R_B - k_2(B_{EC} - B_{IC}) \tag{9}$$

and the corresponding CO_2 buffer or dissociation equation including the Haldane effect is

$$W_{EC} = BS_{EC} - \beta_{EC} \{pH_{EC} - pHS_{EC}\} + k_3\, Hb(1-S_{VB}) + A_{EC}\, P_{EC} \tag{10}$$

with

$$pH_{EC} = pK_{EC} + \log\left[\frac{W_{EC} - A_{EC}\, P_{EC}}{A_{EC}\, P_{EC}}\right]. \tag{11}$$

In these equations Q_{EC} represents the blood flow to the tissues (non-brain), R_B represents the net renal generation of bicarbonate, Hb represents the hemoglobin concentration in gram % (g/100 ml blood), S_{VB} represents the fractional oxygen saturation of the hemoglobin, W_{AB} represents the total CO_2 content of arterial blood, and W_{VB} represents the total CO_2 content of venous blood draining the tissues. It is assumed that the venous blood and extracellular space are in equilibrium and Donnan effects are ignored. Then

$W_{VB} = W_{EC}$ and $P_{VB} = P_{EC}$. The slope of the titration curve, β_{EC}, is determined from the plasma and interstitial fluid protein levels and the amount of hemoglobin present in the blood. The relation is

$$\beta_{EC} = \frac{V_P\ PR_P}{V_{EC}} + \frac{V_I\ PR_I}{V_{EC}} + \frac{1.51\ VB\ Hb}{V_{EC}} \qquad (12)$$

where PR_P is the plasma protein concentration, PR_I is the interstitial fluid protein concentration, and Hb is the hemoglobin concentration in blood, all expressed in g% (grams/100 ml), and V_P is the plasma volume, VB the total blood volume, and V_I is the interstitial volume. Typical values for the new parameters are $k_3 = 0.09$, $pHS_{EC} = 7.38$, $A_{EC} = 0.03$, $S_{VB} = 0.7$, $pK_{EC} = 6.1$, $PR_p = 7.0$, $PR_I = 1.27$, $Hb = 15.0$ and $BS_{EC} = 25.5$. With these values a steady state obtains with $P_{EC} = 45.$, $B_{EC} = 25.87$, $R_B = 0.04$ when $Q_{EC} = 4.25$, and $W_{AB} = 25.1$.

For the brain (B) compartment no subdivision into extracellular and intracellular space is assumed. Instead, a cerebrospinal fluid (CSF) compartment is introduced which is able to rapidly exchange CO_2 with the brain by diffusion. A slow exchange (or pumping) of bicarbonate appears possible with the ultimate goal of CSF pH regulation. Thus, no (or only slight) bicarbonate flow seems to occur due to bicarbonate imbalance. Rather, the mechanism is an active extrusion or uptake to return pH to normal after CO_2 diffusion. For the brain, the appropriate balance equation is

$$\frac{d}{dt}[V_B W_B] = MC_B + Q_B(W_{AB} - W_{BVB}) + k_4(P_{CSF} - P_B) + BT \qquad (13)$$

where MC_B represents total metabolic CO_2 production of the brain, and BT represents effective bicarbonate transfer into the brain from the CSF compartment. The CO_2 buffer curve is

$$W_B = BS_B - \beta_B\{pH_B - pHS_B\} + A_B P_B \qquad (14)$$

where the terms have their usual meaning. It is assumed that brain venous

blood (BVB) has the same P_{CO_2} as brain tissue itself, but a buffer curve given by

$$W_{BVB} = BS_{BVB} - \beta_{BVB}\{pH_{BVB} - pHS_{BVB}\} + k_5 Hb(1-S_{BVB}) + A_{BVB}P_B. \quad (15)$$

The cerebrospinal fluid (CSF) compartment is taken to contain a solution of bicarbonate in water that rapidly exchanges CO_2 with the brain by diffusion, and slowly "pumps" bicarbonate to maintain steady state pH. Thus

$$\frac{d}{dt}[V_{CSF}\, A_{CSF}\, P_{CSF}] = k_4(P_B - P_{CSF}) \quad (16)$$

and

$$\frac{d}{dt}[V_{CSF}\, B_{CSF}] = -BT. \quad (17)$$

The pH_{CSF} is then determined from

$$pH_{CSF} = pK_{CSF} + \log\left[\frac{B_{CSF}}{A_{CSF}\, P_{CSF}}\right]. \quad (18)$$

It is assumed that BT is such that pH_{CSF} returns to normal, pHS_{CSF}, with time constant T_{CSF}. Thus, B_{CSF} approaches a steady state value BSS_{CSF} given by

$$BSS_{CSF} = A_{CSF}P_{CSF}10^{(pH_{CSF} - pK_{CSF})}. \quad (19)$$

In this case

$$BT = (BSS_{CSF} - B_{CSF})/T_{CSF}. \quad (20)$$

Typical parameter values for the above equations are $MC_B = 2.25$, $Q_B = 0.75$, $W_{AB} = 25.1$, $W_{BVB} = 28.1$, $k_4 = 0.000365$, $P_{CSF} = 47.8$, $P_B = 47.8$, $BT = 0$, $BS_B = 27.3$, $\beta_B = 28.9$, $pH_B = 7.38$, $pHS_B = 7.38$, $A_B = 0.03$, $BS_{BVB} = 25.1$, $pH_{BVB} = 7.37$, $pHS_{BVB} = 7.37$, $k_5 = 0.3$, $Hb = 15$, $S_{BVB} = 0.66$, $V_{CSF} = 0.1$, $V_B = 1.0$, $A_{CSF} = 0.03$, $T_{CSF} = 1000.$, and $pK_{CSF} = 6.08$.

The buffer power of blood is given by

$$\beta_{BVB} = \frac{V_P PR_P}{VB} + 1.51\ Hb \quad (21)$$

where Hb is the hemoglobin concentration in g/100 ml blood, and PR_P is the plasma protein concentration in g/100 ml plasma. The quantity BS_{BVB} also changes as "effective bicarbonate" is exchanged with cell space through the equation

$$\frac{d}{dt} BS_{BVB} = \frac{R_B - k_2(B_{EC} - B_{IC})}{V_{EC}}. \tag{22}$$

Note that V_{EC} is assumed constant, an assumption which introduces no significant error.

The mixed venous blood entering the lung consists of a weighted average of venous blood from the brain and from the tissue areas. If Q is the total cardiac output

$$W_{MV} = \frac{Q_{EC}}{Q} W_{EC} + \frac{Q_B}{Q} W_{BVB}. \tag{23}$$

Normally $W_{MV} = \frac{4.25}{5.} \times 27.2 + \frac{0.75}{5.} \times 28.1 = 27.3$ meq/l.

In the lung reservoir the mass balance equation for CO_2 is

$$\frac{d}{dt}[V_L F_A] = V_A\{F_I - F_A\} + 0.0269\ Q\{W_{MV} - W_{AB}\}. \tag{24}$$

This equation is derived by neglecting the difference between inspired and expired ventilation. F_A is the volumetric fraction of CO_2 in dry alveolar gas, F_I is the corresponding volumetric fraction in dry inspired gas, V_A is alveolar ventilation in l/min (BTPS), V_L is the effective alveolar volume, and the 0.0269 is a conversion factor which changes meq/min total CO_2 flow to l/min flow at BTPS. In fact

$$22.26 \frac{\text{ml}}{\text{meq}} \times \frac{1\ \text{l}}{1000\ \text{ml}} \times \frac{760}{713} \times \frac{310}{273} = 0.0269$$

since STPD means P = 760 mm Hg, T = 273°K and BTPS means P = 760 - 47 = 713 mm Hg, T = 273 + 37 = 310°K at sea level. The relation between volumetric fraction and partial pressure is

$$P_A = 713\ F_A \tag{25}$$

at sea level. It is assumed that arterial P_{CO_2} equals alveolar P_{CO_2}, P_A.

Then at equilibrium V_A = 5.27 1/min, F_A = 0.056 or P_A = 40. Knowledge of P_A allows computation of W_{AB} through the buffer or dissociation equation

$$W_{AB} = BS_{AB} - \beta_{AB}\{pH_{AB} - pHS_{AB}\} + k_5\, Hb(1-S_{AB}) + A_{AB}P_A. \qquad (26)$$

Here $\beta_{AB} = \beta_{BVB}$ (Equation (21)), BS_{AB} = 23.9, pHS_{AB} = 7.4, k_5 = 0.3, S_{AB} = 0.99, and A_{AB} = 0.03. BS_{AB} changes with the same rate as BS_{EC} and BS_{BVB}

$$\frac{dBS}{dt}_{AB} = \frac{R_B - k_2(B_{EC} - B_{IC})}{V_{EC}}. \qquad (27)$$

alveolar ventilation itself must be determined from a controller equation like

$$V_A = C_1 pH_{AB} + C_2 pH_{CSF} + C_3. \qquad (28)$$

Renal function enters this model only through the net renal generation of extracellular bicarbonate R_B. This includes net reabsorption and net generation through titratable acid and ammonia secretion. The amount of bicarbonate filtered at the kidney is given by

$$\text{AMT. FILTERED} = GFR\,(W_{AB} - A_{AB}P_A) \qquad (29)$$

where GFR is the total glomerular filtration rate. Normally GFR = 0.125 1/min so that the amount filtered is approximately 3 meq/min. If $W_{AB} - A_{AB}P_A$ ($=B_{AB}$) is less than T_M meq/l all bicarbonate is reabsorbed (at P_A = 40 mm Hg, T_M = 24). The value of T_M depends on arterial P_{CO_2} and it is assumed that

$$\begin{aligned} T_M &= 13.12 + 0.272\, P_A, \quad P_A<40 \\ &= 16.72 + 0.182\, P_A, \quad P_A\geq 40. \end{aligned} \qquad (30)$$

Thus if P_A rises T_M rises and bicarbonate level rises buffering pH changes. The bicarbonate lost by not being reabsorbed is

$$BA_L = GFR\{W_{AB} - A_{AB}P_A - T_M\} \qquad (31)$$

if $W_{AB} - A_{AB}P_A > T_M$ and is 0 otherwise.

Normal titrable acid secretion amounts to about 0.013 meq/min while normal ammonia secretion is 0.027 meq/min. The assumption is made that titra-

table acid excretion is 0.13 meq/min if $W_{AB} - A_{AB}P_A < 18$ and that TA = 0 if $W_{AB} - A_{AB}P_A > 24.5$. In between

$$TA = 0.486 - 0.0198(W_{AB} - A_{AB}P_A). \tag{32}$$

The response is assumed instantaneous. Ammonia excretion is assumed to have a steady state maximum of 0.3 meq/min if $W_{AB} - A_{AB}P_A < 18$, but there is a delay associated with attainment of that maximum with time constant T_{NH}. If $W_{AB} - A_{AB}P_A > 24.5$ ammonia excretion is assumed zero. The maximum ammonia excretion then takes the form

$$NH_3M = 1.126 - 0.046(W_{AB} - A_{AB}P_A) \tag{33}$$

otherwise. Actual ammonia excretion is simulated by the equation

$$\frac{d}{dt} NH_3 = (NH_3M - NH_3)/T_{NH} \tag{34}$$

if $NH_3M > NH_3$. If $NH_3 > NH_3M$ then $NH_3 = NH_3M$. This allows a rapid fall in ammonia production.

The basic model is complete. Much is left out and much remains to be discussed in detail. The influence of pH on other body functions has not been mentioned at all. It is this effect on the body that is the prime motivation for studying the systems that regulate pH. Ventilation control was only briefly mentioned. The effect of aldosterone, potassium, and chloride levels was not considered. Such a treatment would be unpardonable were it not meant to be a simple first effort. What remains is actual computer simulation coupled with a delineation of the effects of acid base imbalance on the major controller functions of the body.

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